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ADEQUACY OF RELATIVE AND ABSOLUTE RISK MODELS FOR LIFETIME RISK ESTIMATE OF RADIATION-INDUCED CANCER

by

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ABSTRACT

This report examines the applicability of the relative (multiplicative) and absolute (additive) models in predicting lifetime risk of radiation-induced cancer. A review of the epidemiologic literature, and a discussion of the mathematical models of carcinogenesis and their relationship to these models of lifetime risk, are included. Based on the available data, the relative risk model for the estimation of lifetime risk is preferred for non-sex-specific epithelial tumours. However, because of lack of knowledge concerning other determinants of radiation risk and of background incidence rates, considerable uncertainty in modelling lifetime risk still exists. Therefore it is essential that follow-up of exposed cohorts be continued so that population-based estimates of lifetime risk are available.

RÉSUMÉ

Nous avons examiné l'applicabilité des modèles relatifs (multiplicatifs) et absolus (additifs) pour la prédiction du risque à vie de cancer associé à une exposition aux radiations. Dans ce rapport, nous présentons une revue de la littérature épidemiologique et une discussion des modèles mathématiques décrivant la carcinogénèse, ainsi que la relation entre ces modèles et ceux prédisant le risque à vie de cancer. D'après les données publiées dans ce domaine, le modèle relatif est préférable pour l'évaluation du risque à vie des tumeurs épithéliales non-liées au sexe. Cependant, les incertitudes qui subsistent sur les autres déterminants du risque associé à l'exposition aux radiations et sur les taux d'incidence de base affectent grandement la précision de ces modèles de prédiction de risque à vie. Il est donc essentiel qu'un suivi des cohortes exposées aux radiations soit effectué afin d'évaluer le risque à vie de cancer dans la population en général.

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A. INTRODUCTION

The purpose of this report is to summarize the extent of epidemiological data available to assess the lifetime risk of radiation-induced cancer in humans, and to discuss the appropriateness of the additive and multiplicative models in predicting lifetime risks. Such models are useful in determining public health policy on radiation protection, and in assessing the probability that radiation has played a causal role in cancers that occur in at-risk populations.

B. BACKGROUND

1. Introduction

It has long been recognized that ionizing radiation can cause cancer. Radiation is not believed, however, to be a major cause of cancer, and has been estimated to account for approximately 1% of cancer deaths (1). It is nevertheless important to be able to quantify radiation risk in humans since there are certain groups that are heavily exposed to radiation, either for medical reasons (diagnostic or therapeutic), or because of occupational exposure, for whom the cancer risk may be significant. Estimates of radiation risk are also necessary for formulating public health policy with respect to radiation protection.

There are many problems in quantifying the risk of radiogenic cancer in humans. Radiogenic cancers are histologically indistinguishable from cancers arising spontaneously or from other known causes; therefore, measurement of excess cancer due to radiation can only take place indirectly, on a probabilistic basis. The modes of action of radiation and other carcinogenic exposures are generally not well understood. Comparatively high spontaneous rates of cancer in human populations exposed to radiation result in the "signal-to-noise" ratio being very small. If low levels of radiation exposure are involved, precise direct estimation of risk requires information upon an impossibly large sample of individuals (2). The varying susceptibility of different tissues and the influence of age at exposure make estimates of long-term effects more complex. These, and other difficulties, imply that the prediction of the risk of radiogenic cancer will continue to involve considerable uncertainty.

Statistical models for carcinogenesis are formulated with several objectives which can include: 1) data description, 2) extrapolation, and 3) biological understanding. In this

review we are primarily interested in the prediction of lifetime risk of cancer, and since no human population exposed to a high level of radiation has been followed for a sufficient time, extrapolation is the main purpose of the model. Nevertheless, any valid model for the prediction of lifetime risk must be able to describe data currently available and describe some biologically plausible mechanism. The calculation of lifetime risk of a particular cancer in a population is dependent upon a number of distinct factors which include:

1) the sensitivity of the population;

2) the character of the radiation;

3) the fractionation of the radiation;

4) the mathematic relationship between radiation dose and cancer incidence; and

5) the relationship between exposure and subsequent risk of cancer as a function of age and other factors known to influence the incidence rate.

In this report, we will be concerned with the last of these five questions and in particular, we will discuss the relative and absolute models for cancer risk.

2. Description of the Models

The importance of cancer as a cause of death and disability in developed countries has led to considerable research into the ways in which substances (exposures) can cause this disease. In particular, radiation carcinogenesis has received considerable attention and data collected from experimental and epidemiologic studies has been analyzed using a variety of statistical models. One such model is the absolute, or additive, model of carcinogenic risk which assumes that the incidence of disease attributable to radia-

tion is a constant function of radiation dose which may depend upon host factors (sex, age at exposure, etc.) but is independent of the age at which disease may develop. Mathematically, we may express this model as follows:

> Let $I(t,d)$ be the incidence rate of (a particular) cancer in a (homogeneous) group of age t exposed to radiation dose d at the same time (prior to t), then
>
> $$I(t,d) = I(t,o) + F(d) \qquad [1]$$
>
> where $I(t,o)$ is the "natural" (or usual) incidence rate and $F(d)$ is the incidence rate due to radiation.

This form has been suggested using radiobiological arguments where it is assumed that a single mutation is necessary and sufficient to cause cancer (3). This model also corresponds closely to that used in the epidemiologic analysis of cohort studies.

A second model for the development of radiogenic cancer is the relative, or multiplicative, risk model which may be written as:

$$I(t,d) = I(t,o)\, R(d) \qquad [2]$$

where $R(d)$ is the relative risk associated with dose d. The multiplicative model thus assumes that the incidence rate in exposed individuals is proportional to the rate in unexposed individuals of the same age. The multiplicative model has a similar structure to one (logistic regression) commonly used in the analysis of epidemiologic case-control studies of cancer. It has been argued that relative risk models generally are more appropriate for the analysis of potential carcinogens (4), although few studies have convincingly demonstrated this. Both the additive and multiplicative models may by modified to include latent (and termination) times during (and after) which the likelihood of the development of radiogenic disease is considered to be negligible.

The additive model, therefore, predicts that radiation-induced risk is independent of age at risk, while the multiplicative model assumes that radiogenic risk is proportional to the natural incidence at given ages. This means that, for most types of cancers whose natural incidence rates vary considerably with age, extrapolation of risk beyond the period of observation or application to other populations will result in quite different lifetime risk estimates using the multiplicative model as compared to the additive model.

The absolute and relative risk models are equated here with additive and multiplicative models respectively. More properly they should be termed examples of additive and multiplicative models. The absolute and relative risks models are terms used in the BEIR III report (5), and correspond to the definitions given previously. Other additive and multiplicative models have been used in which F(d) and R(d) are permitted to vary with age at risk (which is the age for which the prediction is being made). Care must be taken in comparing additive and multiplicative models with such structure since they increase the flexibility of each model and can thus diminish the differences between them. In what follows we will use the two sets of terms interchangeably.

A further difficulty lies in the definition of outcome. Both the absolute and relative risk models make predictions about disease incidence rates but they do not indicate how disease is to be defined. Such a definition may seem unnecessary but is important for the consistency of the two models. For example, if two types of cancer obey the additive model then the composite type formed by combining the two also obeys the additive model. However, if two types obey the multiplicative model the combination of the two will not, in general, obey the multiplicative (or the additive) model, unless R(d) (equation [2]) is the same for each type individually. Obviously the converse holds, that is, if the combination obeys the multiplicative model its components will

not, except under the circumstances previously mentioned. The problem mainly arises when it is desired to combine types to achieve greater statistical power. However, it is not really clear whether one should consider any cancer of a single tissue as a single disease or a composite made up of its distinct biological subtypes. This point will be discussed further in the analysis of leukemia.

Most cases of cancer are known, or at least believed, to be caused by several factors, that is, more than one carcinogen. Furthermore, it seems reasonable to assume that in every population, individuals are being exposed to currently unrecognized carcinogens. From this we may conclude that in attempting to apply either the absolute or relative risk models we will always be applying them to groups which have a distribution of (intrinsic) cancer risks. Thus, analogously to the previous discussion the relative risk model will apply to the individual subgroups and to the total group generally only if the relative risk R(d) is the same for each subgroup. As before, the additive model when applicable to the subgroups is of necessity applicable to the overall group without any conditions on F(d) in each subgroup.

3. Assessing the Fit of the Relative and Absolute Models to Data

Unfortunately, fitting either the additive or multiplicative models to any set of data involves selecting the appropriate parameter values (F(d) in equation [1] or R(d) in equation [2]) which best fit that data. Since stochastic variation is an intrinsic part of the carcinogenesis process, a precise fit of either model to human data cannot be expected even if one of them was exactly true. This, in combination with uncertainties in the radiation dose to which individuals are exposed, further "blurs" the ability to distinguish between the models in the analysis. A further practical problem arises in attempting to distinguish between these two models in that under certain circumstances the prediction of the

models over the period of study may not be greatly different. For example, the models only make different predictions over intervals in which the age-specific natural incidence rate of cancer varies substantially. As an example, the age-specific incidence rate of breast cancer in Japanese women does not vary greatly in the 40-60 year age range. The additive and multiplicative models would thus predict a similar age-incidence pattern for radiogenic breast cancer over the age-range 40-60 years.

A persistent difficulty in the determination of the validity of either additive or multiplicative models is the correct specification of factors believed to affect risk. These would include characteristics of the radiation exposure itself (e.g., dose, fractionation, etc.) as well as other factors (e.g. environmental exposures, endogenous factors) known to influence risk. Two general approaches are taken to reduce the possibility of confounding external factors with model selection (either additive or multiplicative). One is to carry out analysis on subjects of the data which have been required to be homogeneous on the relevant factors. The second is to use "grand" statistical models which include all known or suspected factors. The first approach, although useful, is seldom sufficient because of the large number of possible factors. In using the second approach one is faced with the same problem as attempting to distinguish between the additive and multiplicative models, in that the influence of these other factors is not well known and therefore many parameterizations of their effect are possible. Thus in fitting either additive or multiplicative models of radiation carcinogenesis to a particular data set it is also necessary to fit a large number of other factors. The net effect of such analysis is to diminish the ability with which it is possible to distinguish the additive from the multiplicative model. Of particular concern, in this regard, is the modelling of dose effects which are clearly an important and controversial problem. If we assume that

there is no interaction between dose and model (e.g., an additive model for one dose implies an additive model for all doses with the same latent periods, etc) then the incorrect specification of tentative dose-response will not bias the comparison of the additive and multiplicative models. However such errors will decrease the fit of the model to the data so that it will be more difficult to distinguish between the additive and multiplicative models.

Distinguishing between the additive and multiplicative models for radiation-induced carcinogenesis may be achieved formally by fitting each model to the data (with appropriate forms for F(d) and R(d) in equations [1] and [2]) and testing which does best. This procedure is complicated by the necessity of specifying the error structure for each model. The error structure of a model specifies the distribution of statistical deviations from the predicted values (using either the additive or multiplicative model) to be expected in the examination of real data. For example, if the additive model is fitted using usual multiple regression, where the rate of disease is the dependent variable, then this assumes that the random variation of observations is constant for each radiation dosage level and for all ages at irradiation. In contrast, fitting the multiplicative model using binary logistic regression assumes that random variation is related to the magnitude of the rate of disease. Techniques which assess the goodness of fit of a model depend on its assumed error structure as well as its predictive structure (additive or multiplicative). Tests of "goodness of fit" may therefore be misleading if one model has the correct predictive structure but the wrong error structure and vice versa. This type of problem is most simply overcome by fitting a single statistical model which includes a "shape" parameter for the predictive structure and a common error structure. For one choice of this parameter the resulting model is additive whilst for another it is multiplicative (57). This may be considered to be a

"data-driven" selection of the appropriate model in that the shape parameter is selected that accords best with the data and its closeness to either the additive or multiplicative model is assessed.

In addition to the preceding direct methods of examining the validity of the absolute and relative models, it is also possible to examine whether other variables, on which one has data, are in accord with either model. One useful technique is to examine the distribution of the time since exposure to the occurrence of disease in groups defined by radiation exposure (e.g., exposed versus non-exposed). If the relative model is applicable then all groups will have the same cumulative distribution. If the additive model is true then the cumulative distribution will be higher at early times and lower at later times for cancers in which the incidence rate increases with age, and vice versa. In all cases, such comparisons must be made using comparable groups (e.g., similar age and sex distribution) and allowance should be made for any latent period. However, this technique is really only useful in examining the appropriateness of the relative risk model and not of the additive model.

4. Mathematical Models of Carcinogenesis

A second approach to model selection is to use information derived from experimental carcinogenesis, for a variety of physical agents, in order to construct a model for radiocarcinogenesis and determine under what conditions, if any, it leads to a prediction of the additive or multiplicative models.

A large number of mathematical models of carcinogenesis have been proposed in the last forty years. Carcinogenesis may be broken down into a series of distinct processes, each of which must be separately modelled in order to provide a comprehensive description of radiation carcinogenesis. Such a model would include:

1) a description of the target population of cells (those normal cells in which a tumour can develop);

2) the kinetics of the target population;

3) a description of the carcinogen;

4) the interaction between the carcinogen and the target cells;

5) the influence of other co-factors (i.e., hormones, etc.);

6) all of the above for intermediate cells (intermediate between normalcy and malignancy) where appropriate; and

7) the conditions necessary for a malignant cell to develop into a diagnosable tumour.

Obviously, such a description represents a rather "tall order" and it is not surprising that no comprehensive model exists. A number of models exist which describe various stages of the process for a variety of potential carcinogens in animals and man. We will restrict our attention to "input-output" models which attempt to relate the exposure to a carcinogen (input) to the number or likelihood of tumour development (output). These models predict the distribution of tumours using data on the schedule and dosage of carcinogen administration. A common feature of these models is that they contain one or more parameters which must be specified while fitting the model to the data. This is, of course, a common requirement in the application of mathematical models to biologic systems. It implies that such models may not be used to provide numeric predictions of cancer risk in cases where data on the development of the particular tumour in an exposed population are not already available. Thus, the use of these models is to better under-

stand the nature of the processes involved and so be able to make predictions at doses and schedules other than those for which information is available. Of interest in regard to the purpose of this review is to determine whether any of them provide support for the additive or multiplicative models of ionizing radiation risk. Fortunately, in order to do this, one does not require knowledge of all parameter values, but only a knowledge of the mathematical structure of the models.

We will not review all of the previously proposed models in detail, but will concentrate on two models; those of Armitage and Doll (6) and of Moolgavkar and Venzon (7). A comprehensive, non-mathematical review, if now somewhat dated, is provided by Whittemore and Keller (8) and a more selective, up to date, but less comprehensive review is provided by Armitage (9).

C. REVIEW OF MATHEMATICAL MODELS OF CARCINOGENESIS

1. Introduction

It is well recognized that the incidence rates of the majority of cancers increase with age. This has led to two competing, but not mutually exclusive explanations. The first is that the sensitivity of cells to carcinogens increases with age resulting in more tumours at advanced ages. The second is that a cancer cell is formed by a sequence of changes to a normal cell and that the (inevitable) increased accumulation of cells with these changes leads to greater rates of cancer with increasing age. The first hypothesis is open to direct investigation, and although the results of experiments are not unanimous, it does not appear that the susceptibility of rodents to recognized carcinogens increases with age (10). We will, therefore, only discuss the sequential change, or multi-stage, models of carcinogenesis. We will confine attention to two of them, the model of Armitage and Doll (6) and the model of Moolgavkar and Venzon (7).

2. The Model of Armitage and Doll

The suggestion that a tumour was created by a series of changes (mutations) to a single cell was first proposed by Nordling (11). This hypothesis was based on the observation that plots of logarithms of the mortality rate from selected cancers versus the logarithm of age gave an approximate linear relationship. Armitage and Doll (6) developed this hypothesis into a mathematical model of carcinogenesis by making the following assumptions:

1) any cell must pass through k-1 intermediate stages before it acquires all the properties of a malignant cell;

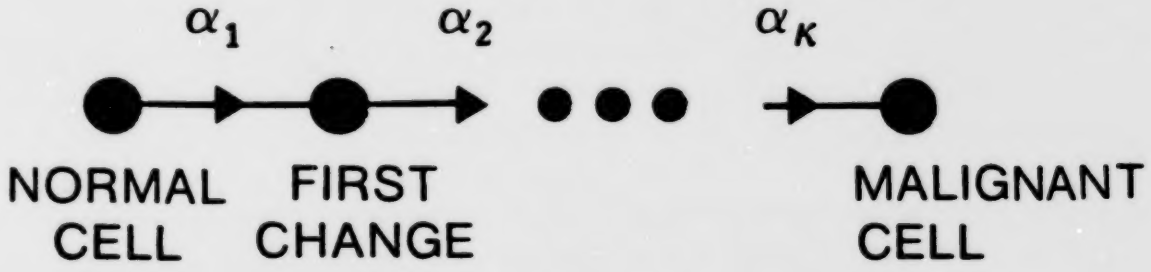
2) changes must occur in a predetermined order;

3) the cell transits between adjacent stages at a rate $\alpha_i(t)$, where t is the individual's age;

4) the rates $\alpha_i(t)$ are "small"; and

5) the time taken for the single malignant cell to grow to a diagnosable tumour is small compared to the time for the first malignant cell to appear.

Schematically, this model may be illustrated as:



By assuming that all the rate parameters $\alpha_i(t)$ were constant, $\alpha_i(t) = \alpha_i$ (do not depend on age), Armitage and Doll (6) showed that the incidence rate of a tumour at age t, I(t,0), is approximately given by:

$$I(t,0) = N\alpha_1\alpha_2\ldots\alpha_k t^{k-1}/(k-1)! \qquad [3]$$

where k-1 is the number of intermediate stages, k is a constant, and N is the number of target cells available for the initial transformation. Taking the logarithm of equation [3], yields:

$$\log I(t,0) = C + (k-1)\log t \qquad [4]$$

where C is a constant. Equation [4] reproduces the linear relationship seen between the logarithm of incidence and logarithm of age which first led to the proposal of the model.

The Armitage-Doll model has been fit to incidence and mortality data for a number of different tumours (6,12). The

fit of the model is reasonably good for epithelial tumours arising in non-sex specific organs but is generally poor for other tumours. However, even for the epithelial tumours there appears to be a deficit in the number of cases at advanced ages compared to what would be predicted. It has been suggested that this may be due to underdiagnosis at advanced ages (12); however a deficit in the number of cancers is implicit in the model if the exact probability function is used rather than the approximation of equation [3] (13). The effect of carcinogens is envisioned as causing changes to at least one of the rate parameters at some time during first exposure to the carcinogen. Armitage and Doll (6) recognized that equation [3] would not apply to two important cases:

1) situations when either the number of target cells, N, or the transformation rates vary naturally throughout life, as in cases of hormonally dependent sites; and

2) cases where individuals are differentially exposed to a carcinogen during life so that the rate parameters are not constant.

The Armitage-Doll model has been extended by several authors (8,14,15) to cases in which subjects experience exposure to a carcinogen during their life. In all cases, the carcinogen is assumed to increase the magnitude of one or more of the rate parameters. In cases where the carcinogen produces a constant change in one or more of the rates throughout the individual's life, the rate parameters may be written as $\alpha_1(d),\ldots,\alpha_k(d)$ where d is the uniform dose-rate of the carcinogen. From equation [1], we have that the incidence rate in exposed individuals I(t,d), is simply given by:

$$I(t,d) = N\alpha_1(d)\alpha_2(d)\ldots\alpha_k(d)t^{k-1}/(k-1)! \qquad [5]$$

By taking the ratio of equations [5] and [4] we obtain

$$\frac{I(t,d)}{I(t,0)} = \frac{a_1(d),\ldots,a_k(d)}{a_1,\ldots,a_k}$$

for which it is seen that the Armitage-Doll model predicts that disease incidence rates in exposed and unexposed populations should be proportional for this very simple situation (i.e., constant rate parameters throughout life). For this situation, the Armitage-Doll model therefore predicts the relative risk model and not the absolute model.

It is important to notice that this relationship does not depend upon how radiation effects any of the rate parameters (except that it is constant throughout life) so that the effect could be linear, quadratic or any other function. If the rate parameters are not constant throughout life then it is not possible to say exactly what the resulting relationship of the incidence rates in irradiated and non-irradiated groups would be.

The method of simulating the effect of radiation on a carcinogen using the Armitage-Doll model is to assume that a carcinogen affects one or more of the rate parameters causing the changes, which the parameter reflects, to occur at an increased rate for the duration of exposure. If each stage of the model is considered to reflect a single distinct change in the genetic material of the cell then radiobiological consideration would suggest that the effect on this parameter would be proportional to the sum of linear and quadratic components in dose absorbed (3). If this assumption (that the Armitage-Doll rate parameters reflect genetic damage) is true then we would expect that analysis of data using a relative risk model would reveal polynomial effects in dose up to the point where cell-killing occurs. Most radiation exposure to human populations does not occur uniformly throughout life but occurs over some shorter interval. For most medical exposures we may idealize it as occurring during an instant and may calculate its predicted

affect in the Armitage-Doll model. If exposure occurs at age t_0 and is assumed to change the rate parameter of the ith-stage then the incidence rate I(t,d)-I(t,0) at (later) age t is approximately given by (14,16):

$$I(t,d) - I(t,0) \propto (\alpha_i(d) - \alpha_i)(t-t_0)^{k-i-1} t_0^{i-1} \quad \text{for } i<k$$

$$I(t,d) - I(t,0) \propto \delta(t_0) t_0^{k-1} \quad \text{for } i=k \qquad [6]$$

This relationship states that the expected increase in cancer incidence due to radiation exposure is related to the age at exposure (t_0) and the time since exposure ($t-t_0$).

This is not compatible, in general, with the absolute model since this model required that the excess incidence does not depend upon the age at detection. Similarly, equation [6] also does not fit the relative risk model since it demonstrates that the relative risk is also dependent upon the age at detection. However, if the carcinogenic exposure affects the final stage alone, then the incidence rate at a sufficiently later time is unchanged. This follows because our definition of tumour incidence has not included the growth time of the tumour. Thus, the creation of a single tumour cell is considered synonymous with the diagnosis of a tumour. The real difference in these two qualities may be removed by assuming the time between the creation of the first tumour cell and diagnosis to follow some distribution and adjusting the age accordingly. After making this adjustment, we would then expect a carcinogen acting upon the final stage to demonstrate a pulse of radiogenic cancers. Observation from most of the major studies of radiation carcinogenesis involving a single exposure (25) for epithelial tumours in humans indicates that induced tumours are seen at the longest available follow-up times. This indicates that the last stage of a multi-stage carcinogenic process is not the only stage affected.

It is possible to consider more complex exposure patterns and effects. For example, Whittemore and others (14,16) have

considered situations for which exposure to radiation is constant for some fixed interval. This leads to equations in which the radiogenic effect is dependent upon the duration of exposure, the time of first exposure, and the interval since exposure. As in the case of the instantaneous exposure, the dependence of the excess cancer incidence upon age at irradiation, duration of irradiation etc. are incompatible, in general, with either the absolute or relative risk models. In general, it may be concluded that for most cases of practical interest, where radiation exposure does not occur uniformly throughout life, that the Armitage-Doll model predicts a pattern of radiogenic cancer which is not compatible with either the absolute or relative risk models.

As previously noted, any human population is made up of individuals who have varying risks of cancer of any particular type (in any situation of practical interest). This may be expected to arise from exposure to other known carcinogens, either exogenous (originating in the environment) or endogenous (specific to the individual). This effect may be explored using the Armitage-Doll model by assuming the population of interest to contain individuals with varying values of the rate parameters. In all cases where constant exposure to all carcinogens (including radiation) occurs throughout life, the effect of radiation will follow the relative risk model (17). Similarly in situations where (possibly the varying) exposures do not influence any of the rate parameters affected by radiation (where exposure occurs throughout life) then the resulting incidence rate will be predicted by the relative risk model. However, if the time varying exposures (other than radiation) influence one or more of the parameters influenced by radiation then the resulting incidence rate will no longer agree with the predictions of the relative risk model.

The previous discussion of the Armitage-Doll model has centered on formulae which are approximations of the exact

expressions and thus the conclusions drawn must be viewed as being approximately true. This raises the question as to whether mathematical identity is a reasonable criteria to apply for agreement. Possibly one should be interested in whether agreement between either (absolute or relative) model and the Armitage-Doll model was reasonable. In view of the form of equation [6] we may reject the notion of reasonable agreement since we have, for exposures of short duration, that the incidence of radiogenic cancer will depend on the age at irradiation and on the elapsed time since irradiation.

The Armitage-Doll model is not, however, an acceptable model alone. Criticisms of the model include:

1) most tumours which fit the Armitage-Doll model indicate values for k in the range 4-7. There is little biological evidence for the existence of such a large number of separate changes required for carcinogenesis.

2) The Armitage-Doll model does not allow for replication and growth of the target cells, or of the transformed cells.

3) The Armitage-Doll model does not fit the observed incidence patterns of many of the tumours of the sex-specific organs even after allowance for possible cohort effects.

4) The Armitage-Doll model does not permit satisfactory modelling of the initiation-promotion process whereby some physical agents are found to greatly increase cancer in animals when applied with other known cancer-causing substances but have no effect on their own.

The above criticisms lead to a number of alterations to the Armitage-Doll theory. Armitage and Doll proposed a two stage

(k=2) model (18) in which the normal cells are in stage 0, transformed cells in stage 1, and malignant cells are in stage 2. In this model, intermediate cells were assumed to grow exponentially. Fisher (19) proposed a similar model in which intermediate cells grew quadratically. Rather than discuss these in detail, we will now describe a model, proposed by Moolgavkar and Venzon (7), which satisfies the previous criticisms of the Armitage-Doll model.

3. The Model of Moolgavkar and Venzon

In common with the model of Armitage and Doll, the model of Moolgavkar and Venzon assumes that a cancer cell develops as a result of a series of sequential alterations in a cell line. In this case, it is assumed that a cell may be classified in one of three mutually exclusive states:

1) normal state - cells in a healthy individual begin life in this state;

2) intermediate state - cells are randomly and irreversibly transformed from the normal to the intermediate state. There cells proliferate with their own kinetic laws but are not malignant; and

3) malignant state - cells in this state have all the properties of cancer cells. They result in the development of a tumour with probability 1.

Features included in this model but not contained in the Armitage-Doll model are:

1) growth of the target normal tissue;

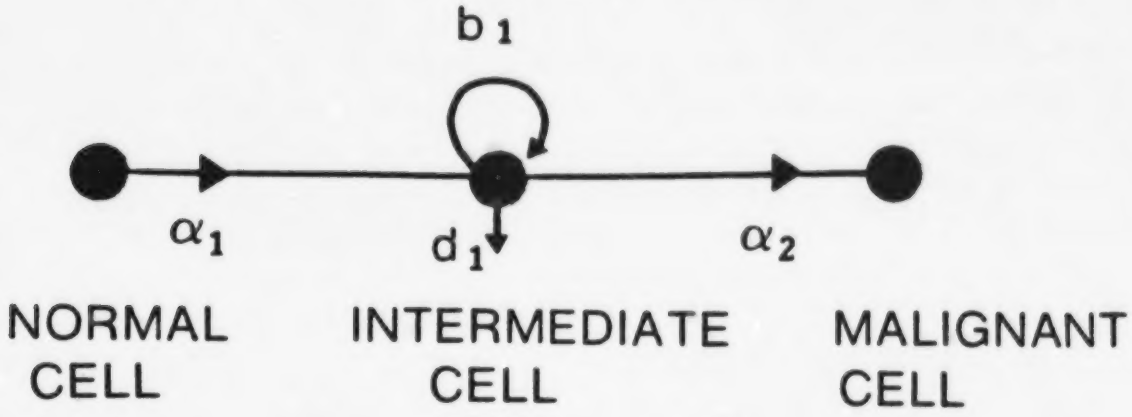
2) growth of the intermediate cells; and

3) regulation of growth by exogenous and endogenous factors.

The regulation of cell growth by endogenous factors permits

better modelling of cancers of sex-specific tissues and the effect of exogenous factors on cell growth permits the inclusion of carcinogens which behave as promoters rather than initiators. The Moolgavkar-Venzon model is best viewed as a generalization of the Armitage-Doll two stage model since the fundamental structures of both models are similar.

Schematically, the process may be illustrated as follows:



α_1 (α_2) represents the spontaneous rates at which normal (intermediate) cells become intermediate (malignant). Little specific meaning is attached to the intermediate state in general. b_1 and d_1 represent the rates at which the intermediate cells spontaneously divide to form undifferentiated and differentiated cells respectively. In specific cases, it may be possible to associate this hypothesized state with an observable state; i.e., hypoplasia and lung cancer. Malignant cells are assumed to proliferate indefinitely without death or differentiation.

Calculation of the incidence rate is best done by first calculating the probability generating function. Since this necessarily involves some mathematical manipulation we will defer the development to Appendix A. (Also see Moolgavkar and Venzon (7); Moolgavkar and Knudson (20)). The incidence is given by

$$I(t,0) \propto \int_0^t \alpha_1\alpha_2 X(s)\, \exp[(b_1 - d_1)(t-s)]ds \qquad [7]$$

where k is a constant (see Appendix A).

Excluding the number of rate parameters, we see that the principal difference between the Armitage-Doll model and the Moolgavkar-Venzon model is the form of the age dependence of the incidence rate. In the Armitage-Doll model the incidence rate is a power function of age (for all tumours) whilst the form of the Moolgavkar-Venzon model is more complex depending upon the growth function of the (normal) target tissue. By choosing appropriate forms for X(t) (the growth function of the normal tissue) it is possible to generate incidence rates which are similar to those of the Armitage-Doll model. For example, this model has been used to model lung cancer (20) where X(t) was assumed to follow a logistic curve, a form generally recognized as being appropriate for the growth of normal tissues.

If, as for the Armitage-Doll model, we assume that the effect of a carcinogen (radiation) is to modify the transition rate parameters α_1 and α_2 then if an individual is exposed to a constant dose of radiation per day throughout life we have:

$$I(t,d) \propto \int_0^t \alpha_1(d)\alpha_2(d)X(s)\exp[(b_1 - d_1)(t - s)]ds \qquad [8]$$

where $\alpha_1(d)$ and $\alpha_2(d)$ are the new transition rates.

Comparison of equations [7] and [8] show, under the assumptions stated, that the predicted age-specific rates of cancer in exposed versus non-exposed are proportional, which is compatible with the relative risk model. In this example we are considering radiation to behave purely as an initiator. If, conversely, we consider it to act purely as a promoter, then the effect of radiation is assumed to act on the parameters of b_1 and d_1, which regulate the growth of the intermediate cells. In this case the new incidence rate will not generally be simply related to the incidence rate

in the absence of radiation. Therefore, even in the simple case where an individual is exposed throughout their lifetime, a "promotional" effect will not be compatible (in the Moolgavkar-Venzon model) with either absolute or relative risk effects.

It is also possible to consider the effect of promoters on the target normal tissue. In the Moolgavkar-Venzon model this is not simply modelled as the normal tissue only affects the incidence of cancer through the growth function X(t). In general for adults, the number of target cells does not show a great variation except for some sex-specific organs so that these effects are not easily incorporated. However, we may view the inclusion of X(t) as representing the mitotic activity of the organ so that the effect of a promoter would be to increase the mitotic activity and we can model this by multiplying the size by some function reflecting this. Mathematically we may include this phenomenon by incorporating a term reflecting mitotic activity into the transition rate α_1. Thus agents which are both target cell promoters and initiators may both be incorporated into the transition rate α_1 (21).

As for the Armitage-Doll model, it is possible to examine the effects of exposure to radiation for short durations. The mathematical structure of the Moolgavkar-Venzon model does not permit the straightforward identification of the effect of radiation exposures for shorter periods and this must be done numerically. The details of the necessary computation are contained in Appendix A. The effect of a continuous exposure beginning at some time (after birth) is to split the incidence into the sum of two terms. If the effect of radiation is assumed to be an initiator that changes the first rate parameter α_1, then only one of these terms is affected. If the exposure occurs at a sufficiently early age, then this second term dominates and subsequent incidence is proportional to population rates. If the radia-

tion exposure occurs late in life, then the carcinogenic effect is small and is no longer proportional to the natural incidence rate. If, alternatively, we assume that the radiation affects α_2 alone then the overall incidence rate in the exposed is proportional to the "natural" rate for all ages at exposure. Alternatively, if we view radiation as behaving as a promoter, then the radiation induced role of disease increases rapidly with age. In this case, the rate of increase with age exceeds that of the natural age-specific rates.

Alternatively, we may consider the effect of short-term exposure to radiation. This may be modelled in a number of ways, however, the most meaningful way is to assume that the radiation causes a proportion of cells to be converted from one state to another. In the case where we assume that normal cells are instantaneously converted to intermediate cells, there is a comparatively rapid rise in the incidence rate which persists throughout life. Although the excess incidence increases throughout life, the rate of increase is not as great as that of the natural incidence so that the ratio of these two quantities declines with increasing age. However, generally this decline is not great so that the ratio is approximately constant. Alternatively, if we assume that an "instantaneous" radiation exposure transforms a proportion of intermediate cells into the malignant state, then this creates a "pulse" of tumours soon after exposure (where the delay is governed by the time for a single malignant cell to grow to form a tumour.) It does not seem reasonable to postulate any prolonged promotional effect from short term radiation exposure so that such an effect will not be considered. These general findings will now be illustrated using numerical calculations for lung cancer.

4. Example Using the Model of Moolgavkar and Venzon

In this section, we will calculate some numerical results for the model of Moolgavkar and Venzon. We will use lung

cancer in non-smokers as an example, parameters for which have already been estimated by Moolgavkar and Knudson. In what follows, we will not be concerned with the magnitude of the number of induced cancers, but with the age-specific pattern of the excess disease. For each cancer, we will compare the effect of prolonged and instantaneous exposures. We will consider the effect of prolonged exposure as permanently changing either the transition rate parameters α_1 and α_2, or the intermediate cell growth parameters b_1 and d_1.

4.1 Lung Cancer

Moolgavkar and Knudson have previously presented a simulation using cancer incidence in non-smokers using an analysis presented by Doll. The parameter values before irradiation were estimated by Moolgavkar and Knudson as $\alpha_1\alpha_2 = 3 \times 10^{-14}$, and $b_1-d_1 = 0.067$. We set the parameter values as $\alpha_1 = 3 \times 10^{-7}$, $\alpha_2 = 1 \times 10^{-7}$, $b_1 = 1$, and $d_1 = 0.933$. As noted by Moolgavkar and Knudson, the incidence rate only depends on the product $\alpha_1\alpha_2$ and the difference b_1-d_1 when the respective component parameters are constant throughout life.

In analogy with the previous discussion of the Armitage-Doll model, we assume that the parameter α_1 and α_2 measure (indirectly) mutations in cells so that we expect that one (or possibly both) will have components which are linearly and quadratically dependent upon dose. In the following simulations, we will assume that the dose is fixed so that the parameters after irradiation are fixed but differ from their pre-irradiation values.

Tables C1a - C1c contain the results of simulations of lung cancer for continuous exposure beginning at three different ages: birth, 25 years old, and 50 years. In each case, the time taken for a tumour to grow to a clinically detectable size is ignored, so that the incidence rate should be interpreted as the rate of creation of the first malignant cells.

Table C1a. Simulation using the model of Moolgavkar and Venzon. Projected age-specific incidence rates of lung cancer (in non-smokers) for individuals continuously exposed to radiation at the same age.

Prior to irradiation $\alpha_1 = 3 \times 10^{-7}$, $\alpha_2 = 1 \times 10^{-7}$, $b_1 = 1.0$, $d_1 = 0.933$

After irradiation $\alpha_1 = 6 \times 10^{-7}$, $\alpha_2 = 1 \times 10^{-7}$, $b_1 = 1$, $d_1 = 0.933$

Age Irradiation Commenced	Age at Risk	Incidence Rate Unexposed/ 100,000	Incidence Rate Exposed/ 100,000	Difference/ 100,000	Ratio
Birth	20	0.6	1.2	0.6	2.0
	30	1.6	3.3	1.6	2.0
	40	3.6	7.3	3.6	2.0
	50	7.5	15.0	7.5	2.0
	60	15.1	30.2	15.1	2.0
	70	29.9	38.6	29.9	2.0
25	30	1.6	1.8	0.2	1.2
	40	3.6	4.4	0.8	1.2
	50	7.5	9.5	1.9	1.3
	60	15.1	19.3	4.2	1.3
	70	29.9	59.9	8.7	1.3
50	60	15.1	15.5	0.4	1.0
	70	29.9	31.2	1.3	1.0

Table C1b. Simulation using the model of Moolgavkar and Venzon. Projected age-specific incidence rates of lung cancer (in non-smokers) for individuals continuously exposed to radiation at the same age.

Prior to irradiation $\alpha_1 = 3 \times 10^{-7}$, $\alpha_2 = 1 \times 10^{-7}$, $b_1 = 1.0$, $d_1 = 0.933$

After irradiation $\alpha_1 = 3 \times 10^{-7}$, $\alpha_2 = 2 \times 10^{-7}$, $b_1 = 1.0$, $d_1 = 0.933$

Age Irradiation Commenced	Age at Risk	Incidence Rate Unexposed/ 100,000	Incidence Rate Exposed/ 100,000	Difference/ 100,000	Ratio
Birth	20	0.6	1.2	0.6	2.0
	30	1.6	3.3	1.6	2.0
	40	3.6	7.3	3.6	2.0
	50	7.5	15.0	7.5	2.0
	60	15.1	30.2	15.1	2.0
	70	29.9	59.8	29.9	2.0
25	30	1.6	3.3	1.6	2.0
	40	3.6	7.3	3.6	2.0
	50	7.5	15.0	7.5	2.0
	60	15.1	30.2	15.1	2.0
	70	29.9	59.8	29.9	2.0
50	60	15.1	30.2	15.1	2.0
	70	29.9	59.8	29.9	2.0

Table C1c. Simulation using the model of Moolgavkar and Venzon. Projected age-specific incidence rates of lung cancer (in non-smokers) for individuals continuously exposed to radiation at the same age.

Prior to irradiation $\alpha_1 = 3 \times 10^{-7}$, $\alpha_2 = 1 \times 10^{-7}$, $b_1 = 1.0$, $d_1 = 0.933$

After irradiation $\alpha_1 = 3 \times 10^{-7}$, $\alpha_2 = 1 \times 10^{-7}$, $b_1 = 1.0$, $d_1 = 0.866$

Age Irradiation Commenced	Age at Risk	Incidence Rate Unexposed/ 100,000	Incidence Rate Exposed/ 100,000	Difference/ 100,000	Ratio
Birth	20	0.6	0.8	0.2	1.3
	30	1.6	2.8	1.1	1.7
	40	3.6	8.0	4.4	2.2
	50	7.5	22.4	14.8	3.0
	60	15.1	61.2	46.1	4.0
	70	29.9	166.2	136.2	5.5
25	30	1.6	1.9	0.3	1.2
	40	3.6	5.7	2.1	1.6
	50	7.5	16.1	8.6	2.1
	60	15.1	44.2	29.1	2.9
	70	29.9	120.2	90.3	4.0
50	60	15.1	20.9	5.8	1.4
	70	29.9	57.4	27.4	1.9

Tables C1a and C1b show the effect expected where radiation is assumed to increase the first and second transition rates respectively. It can be seen that the ratio of the incidence rates in exposed compared to unexposed is fairly constant while the difference in these rates is not. This suggests that such exposure is more likely to produce incidence patterns which are compatible with the relative risk model and not with the absolute model. Table C1c presents the results where it is assumed that radiation acts purely as a promoter. This produces increases in the incidence rates of tumours which depends upon age at risk in such a fashion that the predicted rates are not compatible with either the relative risk or absolute models.

Table C2 provides simulated results for an instantaneous dose of radiation. In this case it is assumed that a proportion of sensitive cells is instantaneously converted into the intermediate state. Examination of the differences and ratios in these tables show that the radiogenic effect is slightly submultiplicative, but clearly the difference column shows it to be superadditive. In practice the ratio is reasonably constant, especially for exposure at older ages, so that the relative risk model holds approximately.

Analysis of the model of Moolgavkar and Venzon shows that under a number of reasonable assumptions (radiation behaves primarily as an initiator) the resulting effect on cancer incidence (for lung and similar epithelial cancers) is likely to be in accord with the relative risk model and not with the absolute model. This conclusion will also generally hold in the presence of other carcinogens which behave as promoters although the time and duration of exposure to these other factors will perturb the resulting age-incidence pattern. This model has not been applied to a wide variety of tumours although it has proved successful in explaining the epidemiologic pattern of some sex-specific tumours (i.e., breast cancer (21)). Recently this model has been

Table C2. Simulation using the model of Moolgavkar and Venzon. Projected age-specific incidence rates of lung cancer (in non-smokers) for individuals receiving a pulse of radiation at a specific age.

Parameters $\alpha_1 = 3 \times 10^{-7}$, $\alpha_2 = 1 \times 10^{-7}$, $b_1 = 1.0$, $d_1 = 0.933$

Proportion of sensitive cell converted to intermediate $p = 4 \times 10^{-5}$

Age at Irradiation	Age at Risk	Incidence Rate Unexposed/ 100,000	Incidence Rate Exposed/ 100,000	Difference	Ratio
Birth	20	0.6	1.4	0.8	2.2
	30	1.6	3.1	1.5	1.9
	40	3.6	6.5	2.9	1.8
	50	7.5	13.2	5.7	1.8
	60	15.1	26.2	11.1	1.7
	70	29.9	51.6	21.7	1.7
25	30	1.6	7.2	5.6	4.4
	40	3.6	14.5	10.9	4.0
	50	7.5	28.8	21.3	3.8
	60	15.1	56.8	41.7	3.8
	70	29.9	111.4	81.4	3.7
50	60	15.1	22.9	7.8	1.5
	70	29.9	45.2	15.3	1.5

used to analyze results from epidemiologic studies of breast cancer (22) and provided a better fit than the usual logistic model.

5. Summary

There exists no generally accepted mathematical model for carcinogenesis. The two models discussed (Armitage and Doll, Moolgavkar and Venzon) represent the current "state of the art" in general models of carcinogenesis, although others exist for specific tumour types. By assuming radiation to behave primarily as an initiator, consideration of both these models generally imply that the effect of radiation will be to increase the age-specific incidence rate of cancer by an amount which is approximately proportional to its "natural rate". In some situations (Armitage and Doll model) this conclusion depends on the time at which radiation exposure occurs and at what age disease occurs. In no case do either of these models (under reasonable assumptions about the behaviour of carcinogens) lead to predictions in accord with the absolute model. Both these models, under certain circumstances, lead to predictions that the relative risk may decline somewhat with time since exposure. It will therefore be important to analyze radiogenic data with a view to this possibility so that any departure from the relative risk model can be detected.

D. EPIDEMIOLOGIC DATA ON RADIOGENIC CANCER

Ideally, epidemiologic studies of radiation and cancer should fulfill certain requirements in order to be useful in assessing relative and absolute models of lifetime cancer risk. These requirements are as follows:

1) The exposed and comparison groups should be well-defined, both in terms of likelihood of exposure and in characterization of other population variables that may confound the measurement of the effects of radiation.

2) The exposed population should be representative of other classes of the population, so that the results of analysis can be generalizable.

3) There should be sufficient numbers in both exposed and comparison groups to allow for adequate assessment of outcome in both groups.

4) Follow-up should be adequate over a period in which the natural incidence of cancer varies substantially.

5) Analysis of the data should be available using both models, since in general the analysis cannot be carried out post-hoc.

6) Most importantly, it is necessary that the analysis of each study present results on the development of cancer by age and by time since exposure, since it is on such age and time-specific effects that the two models can be compared.

Unfortunately, comparatively few sets of data provide the necessary information to permit a comparison of the two models. These are summarized in the following sections by individual cancer site.

1. Lung Cancer

The human respiratory tract is exposed to all inhaled gases from natural or man-made sources in the environment. Lung cancer rates resulting from such exposures vary from around 25 per 100,000 in China, India, and some Latin American and African countries, to over 100 per 100,000 in areas of western Europe and North America (23). In North America, lung cancer accounts for approximately 15% of all new cancer cases, and 25% of cancer deaths. Three times as many males as females develop the disease, although this ratio is changing, as female incidence is rapidly increasing while male incidence is stable or declining. Cigarette smoking is the predominant risk factor and accounts for much of the male/female difference in incidence, with occupational exposure to chemicals and radiation also strongly influencing risk of the disease. The lung is one of the most sensitive organs in the human body with respect to radiation-induced carcinogenesis, as is evidenced by the experience of uranium miners in the Schneeberg-Jachymov region for over 400 years (24) and by the rapid change in incidence with changes in smoking prevalence in this century.

There are two sources of radiation to which human populations have been primarily exposed:

1) acute external exposure to x-rays, gamma rays and neutrons; and

2) chronic exposure to alpha irradiation through inhalation of radon and its short-lived radioactive daughter products.

The two population groups acutely exposed to external radiation that are large enough and have enough years follow-up to provide quantitative information on long term cancer risk are the Japanese atomic bomb survivors, who received whole

body radiation exposure to gamma rays and neutrons (25), and British ankylosing spondylitis (AS) patients aged 20 and above treated with x-rays (partial body exposure) from 1935 to 1954 (26,27). The characteristics of these study populations are shown in Table D1. Both groups received an acute (time-limited) exposure to radiation. An analysis of long-term cancer mortality in the AS patients is contained in the paper by Smith and Doll (26), where a subset of the original group that had received a single course of treatment was followed. The mean bone marrow radiation dose for these patients was 347 rads, with a standard deviation of 187 rads. Among the atomic bomb survivors, followed by the Radiation Effects Research Foundation (RERF) in the Life Span Study (LSS), 87.5% of the exposed cohort with known levels of exposure have been estimated to have experienced whole-body irradiation in the 1 to 99 rad range; 6.5% had estimated exposure in the 100-199 rad range; 2.9% had exposures from 200-299 rads; and 3.2% had 300 or more rads exposure, using the T65 dose estimates and adjusting fractional values to the closest rad (25). These estimates are still somewhat uncertain due to difficulties in characterizing the quality of the radiation output from the two nuclear bombs.

Among groups chronically exposed to alpha-irradiation, which include studies of underground uranium, fluorspar, and metal ore miners, three large cohorts of uranium miners, from Ontario, Canada (28,29), U.S.A. (30,31), and Bohemia, CSSR (32,33), have provided data on the long-term effects of radiation. These miners were chronically exposed to radiation for varying lengths of time. A comparison of the study population is shown in Table D2. The Rn daughter exposure of the miners is measured in working-level months (WLM), where a working-level (WL) is defined as "any combination of short-lived radon daughters in 1 litre of air that will result in the ultimate emission of 1.3×10^5 MeV of potential alpha energy" (34). Exposure to 1 WL of radon daughters for 170 working hours is taken to be 1 WLM.

Table D1. Characteristics of irradiated populations examined for lung cancer mortality.

Investigators:	Kato, Schull	Smith, Doll
Population:	Atomic bomb survivors from Hiroshima and Nagaski	Ankylosing spondylitis patients receiving X-ray therapy
Number of subjects exposed:	50,661	14,111
Type of exposure:	single; gamma and neutron rays	Single, X-rays
Number of years follow up:	29 yrs (34 yrs after exposure)	16.2 years (mean)
Percent follow up:	99%	98.5%
Person-years at risk:	2,622,000	133,874
Number of cases (deaths):	459	124
Mean dose:	+	347 (mean bone marrow dose)

+ Not reported

Table D2. Characteristics of study populations in three uranium miners series.

Investigators:	Muller et al., 1983, 1984	Whittemore et al., 1983 Waxweiler et al., 1981	Kunz et al., 1979 Sevc et al., 1976
Population:	Uranium miners, Ontario, Canada	White uranium miners, U.S.A.	Uranium miners, Czechoslovakia
Number of subjects exposed:	15,984	3,362	2,433 (Group A)
Type of exposure:	Cumulative; short-lived radon-22 daughter products	same	same
Median number of years of follow up:	18 years (1955-1981)	19 years (1950-1977)	26 years (1949-1975)
Percent follow up:	94%	>99%	+
Person-years at risk:	241,942	62,556	60,000
Mean level of exposure:	53.5 WLM	+	+
Median age at start of exposure:	approx. 25 years	30 years	35-40 years

+ Not reported

Whereas the AS patients were exposed to low-LET radiation, and the uranium miners' exposure was to high-LET radiation, the atomic bomb survivors received a mix of high (neutrons) and low (gamma rays) - LET radiation. Since the extent of the neutron component of the two bombs is still uncertain (particularly in Nagasaki) it is difficult to determine the effect of high-LET radiation in this cohort.

The results of the studies of external radiation will be reviewed first, with a discussion of the uranium miners' studies following.

1.1 Lung Cancer from External Radiation

1.1.1 Life Span Study of Atomic Bomb Survivors

The Life Span Study (Extended) cohort consists of approximately 82,000 atomic bomb survivors including 50,600 exposed individuals from both Hiroshima and Nagasaki. The Radiation Effects Research Foundation has published data covering a follow-up period of 29 years, from 1950 (five years after exposure) to 1978 (38 years after exposure) (25). Approximately 20,300 individuals from the cohort are from Nagasaki, and this group is younger than the Hiroshima subjects (by about five years on average).

There are several characteristics of this study that make it a reliable source for the assessment of long-term cancer risk due to radiation. There is a large number of subjects in the cohort, over the total age range, and these subjects were not selected for medical reasons or other cancer risk factors. A wide range of radiation dose is represented. Follow-up has been comprehensive, particularly for mortality, and some 70% of cancer deaths can be confirmed. The principal uncertainties relating to the results are the lack of information relating to absorbed dose, and the relative contributions of high and low LET radiation, and the possible differences in their effects on long term cancer mortality.

The important results from this study in regard to lung cancer are as follows:

1) lung cancer mortality increased with increasing radiation dose;

2) excess lung cancer mortality is evident (and appears to increase) throughout the follow-up period;

3) the latent period, that is, the time interval until excess lung cancer mortality becomes apparent, increases with decreasing age at time of bomb (ATB), and is not affected by dose; and

4) the radiation-induced cancers develop at the same age for both the irradiated and the non-irradiated group.

There were some differences between the Hiroshima and Nagasaki subjects; in particular, the excess seen in Nagasaki was not as large nor as consistent over time as that in Hiroshima. This may be because of the differences in the radiation components of the two bombs. However, the main conclusion of this latest analysis of the LSS cohort with respect to lung cancer mortality is that the results support the relative risk model of carcinogenesis more strongly than the absolute risk model. Some members of the cohort are only now reaching the ages at which cancer risk can be detected; further follow-up is necessary in order that their cancer experience can be compared with that predicted from the relative risk model.

1.1.2 Ankylosing Spondylitis Study

The cohort for the ankylosing spondylitis study consists of over 14,000 patients treated with x-rays between 1935 and

1954 in Britain and Northern Ireland. The latest published results, which will be reviewed here, relate to a group of patients treated with a single course of therapy and followed to the end of 1969 (26), with a mean follow-up period of 16 years, starting approximately nine years after exposure. Apart from the fact that the population was selected for medical reasons, this study has many of the advantages of the Life Span Study. It too has a relatively large study population with a large age range represented, although there were no children in the study. Follow-up has been lengthy and only 1.5% of the patients have been lost to follow-up. Furthermore, estimates of bone marrow dose were made for a sample of patients treated.

In this study mortality rates were compared with age- and sex-specific mortality rates for England and Wales. In a separate study to validate the use of population-based rates, the cancer mortality experience for a group of 1000 AS patients not given x-rays was compared with national rates and found to be similar (35). The use of population-based rates, therefore, seems to be justified in this study.

The following results were obtained with respect to lung cancer:

1) the excess cancer mortality from heavily irradiated sites (including lung cancer) apparently increases after three to twenty years of follow-up; a non-significant drop is observed after twenty years;

2) excess cancer death rates from heavily irradiated sites increased with higher age at first treatment; and

3) for patients first irradiated at different ages, the subsequent risk of dying of cancer was approximately proportional to the expected death rate for a non-irradiated population.

As remarked in Section B, if the relative risk model applies to cancer of individual sites, it will not necessarily apply to those sites aggregated into a single classification. In this analysis where sites with different patterns of age-incidence have been aggregated, it will only apply if the relative risk (for the absorbed dose) is the same for each of the irradiated sites. It seems unlikely that this is true since the relative risks in this group range between 0 for skin to 7.84 for CNS tumours in the period three or more years after first treatment. This being said, lung cancer dominates this group (contributing 49% of the cases) so that the contribution of the sites with quite different relative risk is quite small. These difficulties do not affect the absolute model since the aggregated group should also be "additive", as long as the latent periods, etc., are the same for each site. The excess risk is seen to vary greater proportionately than the relative risk so that this study may be said to provide evidence against the absolute model and some tentative evidence for the relative risk model. However, the calculated values of excess risk are more unstable than those of relative risk so that this interpretation must not be given excessive weight.

1.2 Lung Cancer from Internal Radiation

1.2.1 Ontario Miners' Study

The cohort for the Ontario miners' study consisted of 50,201 (uranium, nickel-copper, iron ore, mixed ore, and gold) miners in the province, of which 15,984 were uranium miners with no asbestos mining exposure (28,29). Workers' records were matched with mortality files from Statistics Canada, and mortality experience of the cohort was compared with that for the male population of Ontario. Workers employed from 1955 to 1967 were included in the study, and their mortality experience was followed to the end of 1981. Of the

three large groups of uranium miners reported, the Ontario study has by far the largest cohort. This group, however, also had the lowest average working period in the mines, with the median number of years in mining totaling 1.5 years.

The results of the study were as follows:

1) lung cancer mortality was elevated among the study group;

2) using an attributable (additive) risk model, a greater risk was found for those miners in an older group (ages 55 years and over) than in a younger age group (under 55 years). However, using a relative risk model the risk was not significantly different;

3) using the relative risk model, the assumption of a latent period of 5 or 10 years does not affect the risk. Using an additive model, the risk increase with a larger latent period; and

4) the data is compatible with both an additive and a relative risk model.

In analyzing data on uranium miners the authors have fit the two models:

$$\text{Attributable Risk Model} \quad I(t,d) = I(t,0) + (A + Bd) \qquad [1]$$

$$\text{Excess Relative Risk Model} \quad I(t,d) = I(t,0)(1 + A + Bd) \qquad [2]$$

Examination of equations [1] and [2] show that these are particular cases of the absolute and relative risk models where the risk functions are assumed to depend linearly on dose (measured in WLM). In order to fit these models individuals were aggregated into groups based on their exposure.

Rate of disease was then regressed, using weights not explicitly stated, against dose. The resulting examination of the fit of the two models is somewhat ambiguous. For example, if the expected incidence rate of bronchogenic cancer is the same in each (dosage) group then the two models are identical although their parameterizations are somewhat different. Thus the finding of no real difference between the fit of the two models may have little or no relationship to the appropriateness of each model. The authors have also examined the two models in miners under 55 and over 55 years of age at time of risk. (Note: the authors use the term age at ascertainment which we take to mean age at risk.) They have then examined whether the parameter B has the same value for both age groups for each of the models. In order to relate their analysis to inferences regarding the absolute and relative risk models it is necessary to assume either 1) the age at exposure does not affect risk of disease or 2) the average age at exposure of the two groups is similar. It seems that the latter is unlikely, by virtue of the study design. Also, age at exposure is recognized to affect subsequent risk so that the results of the analysis cannot be simply accepted at face value. Further analysis using age at first exposure is thus necessary using this data. Similarly, knowledge of smoking history would also be very useful so that some attempt may be made to separate the effects of smoking and radiation in the excess lung cancer seen in this group.

1.2.2 The CSSR Study

The epidemiologic study of lung cancer in Czechoslovakian miners initially identified a cohort of uranium miners employed from 1948 to 1957. Approximately 56%, or 2,433 of the miners, were employed prior to 1953, and this group was subsequently followed and analyzed in terms of their lung cancer experience (32,33). Lung cancer incidence was obtained from industry and government sources to the end of

1975 and compared to national rates for males in Czechoslovakia. Median age at start of employment was between 35 and 40 years, and average exposure time was 10 years. The exposure levels of the total cohort varied from less than 50 WLM cumulative radon daughter exposure to over 600 WLM.

The results of the Czechoslovakian study demonstrate:

1) an excess of lung cancer with cumulative exposure to airborne radiation that increases with increasing doses and time of exposure; and

2) a positive association of radiation-induced lung cancer mortality and age at start of exposure, uncontrolled for age at follow-up.

The authors have published several reports in which the data has been analyzed in a variety of ways. In an earlier report (32) both the excess risk (observed - expected) and risk ratio (observed/expected) per miner were analyzed as a function of radiation dose (WLM). These were further subdivided by the time at which employment commenced (group A: 1948-52; group B: 1953-57). Analysis was also made for group A by dose and by age at first exposure (< 30 years, 30-39 years, >39 years). They found that the excess risk per miner per WLM was quite constant as a function of total dose for those first irradiated prior to 40 years of age but seemed to decline somewhat at higher doses in those first irradiated after 40. No analysis by period at risk was presented so that it is not possible to determine the compatibility of the absolute and relative risk models with this data.

A second analysis of this data (33) was made using an additive model in which the calculated number of excess lung cancers for miners was regressed against cumulative exposure and two measures of exposure pattern: 1) duration of exposure and 2) density of exposure, classified as increasing, uniform or decreasing. Since only a single model was fit it

is difficult to comment whether either model would be a better fit to the data. No analysis was made in which age at exposure was included so that the possible effect of this factor is not addressed. Similarly no analysis is made of the age at risk. The authors do present data indicating that certain histologic types (in particular small cell undifferentiated) are over-represented compared to others. As previously noted (in Section B) the relative risk model implies, if it applies to lung cancer overall, that it will not apply to the individual subtypes (which have varying age-incidence patterns). However, without further information this point cannot be explored.

1.2.3 The U.S. Study

A total of 3362 white and 780 non-white uranium workers employed in the U.S. uranium mining industry from World War II to 1970 were identified and followed from 1950 to 1977 (30,31). This cohort had originally been identified through Public Health Service medical survey records, which included information on radiation exposure and tobacco use. Mortality follow-up was conducted through pension records and industry census data. Vital statistical records provided information on cause of death. The mortality experience of this cohort was then compared to U.S. death rates for white males, adjusted for age and calendar period.

Approximately 14% of the cohort started employment before 1947 and had more than 30 years of follow-up; another 51% of the cohort had accumulated between 20 and 25 years' follow-up. Median age of the cohort at start of employment was 30 years.

The principal conclusions of the study investigators were as follows:

1) lung cancer mortality increased with increasing exposure. The proportionate excess seemed to be

constant for exposures between 120 and 1799 WLM, but an increasing ratio of observed to expected is seen at 1800 WLM and above;

2) both the relative and absolute excess risk peaked in the years 1965-1974; however, only three more years' follow-up was available after that time;

3) an excess of lung cancer mortality was seen five years after start of follow-up; this excess continued throughout the follow-up period of greater than 35 years; and

4) there was no apparent relationship between age-specific cancer mortality rates and age at start of uranium mining, after controlling for total WLM of exposure.

In the analysis of this data by Waxweiler et al (30), observed and expected numbers of lung cancers have been calculated as a function of years of employment (0-4, 5-9, 10-24, 25-29, 30-34, 35+), age at risk (<50, 50-64, 65+) and period (1950-4, 55-9, 60-4, 65-9, 70-4, 75->). Each analysis is reported separately so that it is not possible to separate the effects of each factor. Such a separation is necessary in order to examine the fit of either the absolute or relative risk models since they both predict that excess rates of disease will be a function of these three variables.

1.3 Summary

Although all the studies reviewed report on large populations and have many years of follow-up, they all have limitations that inhibit the validity and/or the generalizability of the results. All the studies suffer from a lack of reliability with regard to individual dose estimates, and from the inability to control for confounding factors, in particular smoking habits. The radiation exposure of the

Japanese cohort consisted of a mix of low and high LET radiation to the whole body, in contrast to the partial-body exposure to a specific type of radiation in the medically or occupationally exposed populations. The studies of occupationally-exposed miners have the additional problem of appropriateness of the control group, and a shorter follow-up time. In spite of these shortcomings, results of the studies were remarkably consistent. The only notable discrepancy was in the relationship between the age-specific rates and the age at exposure found in the different studies. The positive association seen in the Czech miners is inconsistent with the negative association seen among the LSS cohort, and the lack of any relationship in the U.S. miners. The Czech data, however, was not analyzed controlling for age at follow-up, and this may account for the difference.

Although both the LSS study and the study on U.S. miners have shown an increase in lung cancer risk among smokers in their respective cohorts, only the U.S. study had enough data to analyze smoking in terms of a risk model for radiation-induced lung cancer. The results of that analysis (31) demonstrate that lung cancer risk is apparently a product of components due to radiation and smoking. In addition, smoking apparently does not change the age at which the radiation-induced cancer develops.

The results of all the studies of radiation-induced lung cancer reviewed here are compatible with both the absolute and the relative risk models, although there is somewhat more support for the relative risk model. Until the cohorts exposed have been followed until death the exact form of the model remains uncertain.

2. Breast Cancer

Breast cancer is the most common form of cancer among women in the western and industrialized countries, and exhibits

low rates in Asia, Latin America, and Africa (36). It is rarely seen in women under 30, and in western populations, increases to very high rates by age 70, with a plateau at the peri-menopausal ages. In Asia, breast cancer rates decline in the postmenopausal period. Environmental factors such as reproductive practices, socio-economic status, and diet play a significant role in the induction of breast cancer. Because the case fatality rate is around 40-50%, incidence studies are more informative than mortality studies for assessment of risk.

Ionizing radiation was first demonstrated by Mackenzie (37) to cause cancer of the breast in a study of women treated for tuberculosis. Since that time, there have been several studies that have confirmed the sensitivity of the female breast to radiation-induced cancer. Studies of human breast carcinogenesis fall into four main types when classified by reason for irradiation:

1) the Life Span Study (LSS) of atomic bomb survivors;

2) women receiving fluoroscopy treatment for tuberculosis;

3) women irradiated for post-partum mastitis; and

4) women irradiated because of benign breast disease.

Of these types, each consists of a single body of data except for the fluoroscopy series where several studies have been undertaken in the U.S. and Canada.

Because of the need for at least a 20-30 year follow up period on subjects, all studies report observations on individuals irradiated prior to 1970. The medical series consists of women exposed to x-rays produced by equipment operating in the kilovoltage range. Thus, these series examine the risk of women exposed to low LET radiation only.

The LSS includes women exposed to a mix of gamma and neutron radiation which varied between the two bomb sites. Currently, the LSS is the only series for which the relationship of high LET radiation to breast carcinogenesis can be assessed. Given uncertainties in the neutron doses received by individuals, the determination of the effect of high LET radiation is extremely difficult. Studies to date, using the T65 dosimetry, indicate that a RBE of 1.0, for the radiogenic effect of neutrons on breast tissue, cannot be rejected given the available data. In these circumstances, it is not feasible to consider separate lifetime estimates of breast cancer risk for high LET radiation and we will only consider the effect of low LET radiation.

In reviewing the published studies on the relationship between an exposure and the development of disease, one must recognize that the way in which results are reported may not be amenable to comparison using competing models of disease risk. For example, the reporting of disease experience as a rate per cGy-year is clearly compatible with an additive linear dose-response model. Similarly, a change in relative risk for cGy is most compatible with a multiplicative model. Of necessity, we will report results as the authors did, which is not intended to imply anything regarding the underlying mechanism of cancer induction.

The following is a discussion of the fluoroscopy series separately and then the LSS and the other medical series.

2.1 Fluoroscopy Series

A common uncertainty in all the studies relating breast cancer to the use of fluoroscopy, during pneumothorax for the treatment of tuberculosis, is the lack of detailed information on absorbed doses. In all cases, it has been necessary to estimate retrospectively breast doses using general descriptions of patient orientation, exposure times, number of visits, etc. (38,39). In each of the series, the

breast doses were given in a large number of fractions over an extended period. In two studies (40,41), individuals known to be alive were contacted in order to improve estimates of absorbed dose. Two studies report only mortality data (41,42). The study by Davis et al (41) is not in accord with the results of the other two studies in that no excess breast cancer mortality was noted in the exposed population. The reason for this discrepancy is not clear, especially since its methodology and patient population appear similar to those in the other studies. The authors suggest that it may be due, in part, to the age distribution and comparatively low doses absorbed. Since the findings of this study are at variance with the other major studies of radiogenic breast cancer, we will not discuss it in any detail. A description of the irradiated populations is contained in Table D3.

The analysis of data from Massachusetts by Boice and Monson (40) contains four principal results:

1) that the risk of breast cancer increases with increasing dose;

2) that risk is dependent upon age at first exposure with highest risk for those first irradiated in the 15-19 year age range;

3) that the period (latency) before excess risk becomes apparent increases with decreasing age at first exposure; and

4) excess risk continued, and appeared to increase, up to the end of the follow up period.

The results of Howe (42) were essentially in accord with these observations. Of particular interest to the question of the appropriateness of either the absolute or relative risk model is the observation that risk increased with time after first exposure. This observation is consistent with

Table D3. Characteristics of the study populations in the three fluoroscopy series.

Investigators		Boice and Monson, 1977	Howe, 1984	Davis et al., 1987
Number of Women	- exposed	1,047	11,284	2,074
	- unexposed	717	12,034	2,141
Years at Risk	- exposed	28,011	279,795	
	- unexposed	19,025	+	103,154
Cases (Deaths)	- exposed	41	172	24
Mean Dose		150	+	66
Mean Age at Exposure		25	+	28

+ Not reported

the relative risk model which predicts that risk will increase because the "natural" incidence rate of breast cancer increases with age in North American populations.

Both multiplicative and additive models have been fit to the Massachusetts data. In the additive model, risk (incidence rate) was assumed to increase linearly with dose, whereas relative risk was assumed to increase linearly with dose in the multiplicative model. No formal statistical comparison was carried out on the fit of these models to these data and, thus, it is not possible to judge the superiority of either. Visual analysis of the fit of each model led the authors to suggest tentatively that the relative risk model may provide a better fit to the data; however this superiority is clearly not marked. The data of Boice and Monson (40) have also been analyzed incorporating information on known breast cancer risk factors on individuals (43). This analysis demonstrated that radiation in the year of menarche (first menstruation) or of first birth produced an enhanced effect when compared to a similar amount of radiation at other times. Also, individuals with an increasing number of breast cancer risk factors had increased rates of radiation-induced disease although the magnitude of this increase was not regular in the number of risk factors. This last observation, if confirmed, has implications for the calculation of lifetime risk. It implies there is no single additive incidence (for the absolute model) which may be used to calculate lifetime risk. For an individual, the additive incidence due to radiation will depend upon other risk factors for disease. Such a modification of the additive model is not implausible and one may speculate that such an overall incidence rate is, itself, a sum of contributions relating to each individual risk factor. Similarly, for the relative risk model, one would assume the effect of ionizing radiation in an individual who already has breast cancer risk factors to be a product of terms representing the impact of individual factors. A different order of com-

plexity exists, however, because the absolute model would then require estimates of the excess incidence due to radiation for each breast cancer factor separately (as a minimum), whereas only a single estimate of the effect of radiation is required for the relative risk model. Such a structure, if true, would make the calculation of lifetime risks extremely difficult on an individual basis.

2.2 Other Series

2.2.1 Post-partum Mastitis Series

This series (44,45) is comprised of a group of women from Rochester, New York treated for acute post-partum mastitis (and some with breast abscesses) with x-rays. The possible relationship between the reason for radiation and breast cancer risk led to the inclusion of three different control groups: sisters of the cases, women from New York City with acute post-partum mastitis not receiving radiation therapy, and their sisters. All three control groups had a similar incidence of breast cancer and were combined to form a single control group of 993 women. Since radiation was aimed at the breast for therapeutic reasons, not all women had both breasts irradiated (ignoring scatter) and it was possible to analyze the data using breast-years rather than person years. Some characteristics of the study population are given in Table D4. Results are similar to those from the fluoroscopy studies (40,42) in that:

1) the period before excess risk becomes apparent (latency) increases with decreasing age at first exposure;

2) excess risk continues and appears to increase, up to the end of the follow up period; and

3) the distribution of the time from exposure to the diagnosis of breast cancer is the same for the exposed and control groups.

Table D4. Characteristics of irradiated populations examined for incidence of breast cancer.

Investigators		Shore et al., 1986	Tokunaga et al., 1979	Baral et al., 1977
Population		Women with post-partum mastitis	Atomic bomb survivors	Women treated for BBD
Number of Women	- exposed	606	24,179	1,023
	- unexposed	1,239	38,724	
Years at Risk	- exposed	17,800	535,628	30,505
	- unexposed	36,300	829,738	
Number of Cases	- exposed	56	169	115b
Mean Dose		378a	+	715c
Mean Age at Exposure		27	+	36d

a Absorbed dose at 2.5 a below skin.
b In irradiated breasts.
c Estimated median dose.
d Median age.
+ Not reported

There appear to be two areas of disagreement, however, between this study and the results of the fluoroscopy series:

1) incidence increases with dose up to about 400 cGy and then stabilizes or declines.

2) no consistent relationship exists between age at irradiation and subsequent breast cancer risk.

These differences are not necessarily viewed as inconsistencies since the higher risk seen in the fluoroscopy series at younger ages may be due to increased hormonal stimulation (at these ages) which may be comparable with the hormonal stimulation produced by pregnancy present in the post-partum mastitis series. Similarly, the decline in breast cancer risk at high doses may be due to cell sterilization at these doses, an effect which may not have been apparent in the fluoroscopy series because of the much lower dose per fraction used.

The mastitis series has been specifically analyzed using both additive and multiplicative models. The authors found the difference between the expected and observed incidence rates (standardized for age at irradiation) increased with time from irradiation. When a relative risk model was fit, however, no trend was seen and a statistical test for departure from the constant relative risk model was nonsignificant ($p > .6$) (45). This finding is equivalent to the observation that the distribution of time between exposure and disease is the same in the exposed and unexposed groups.

The mastitis series has also been analyzed using information on other known risk factors for breast cancer (46). In their analysis the authors assumed an additive model for the effects of known and suspected risk factors (including radiation) on breast cancer incidence. In order to do this they calculated an index of synergism S due to Rothman (47),

which measures the departure from additivity. Selected results of this analysis are given in Table D5. For the purpose of comparison an index of synergism SR was calculated for the relative risk model which consists of the product of the observed incidence rates in women irradiated with risk factor multiplied by the rate in women non-irradiated without the risk factor divided by the product of the rate in women irradiated without the risk factor multiplied by the rate in women non-irradiated with the risk factor. Results for this index are also presented in Table D5. In each case a value of one indicates the findings are in exact agreement with the appropriate model and values greater than or less than unity indicate findings greater and less than the predicted results respectively. Unfortunately it is not possible to place confidence intervals on these quantities but it is readily apparent that neither model provides a precise fit to the data. Visually, it appears that the additive model may fit the data somewhat better but any superiority is not striking.

2.2.2 Life Span Study

A number of series relating to the risk of breast cancer have been published from the Life Span Study (LSS) of survivors of the Hiroshima and Nagasaki atomic blasts. We will discuss the data presented by Tokunaga et al (48) and reanalyzed by Land et al (49). As may be expected, some uncertainty exists as to the absorbed doses of individuals in this population. In particular, the Hiroshima bomb is believed to have delivered 10-30% of the radiation from neutrons. Differences in the biological effectiveness of neutrons in producing tumours could produce different dose-response curves for the two populations. No difference was noted in the analysis reported here although the calculation of neutron doses used (T65) is currently being revised which may cause this finding to be changed. The LSS study is the largest series currently available and has a well-defined

Table D5. Indices of synergism for the mastitis series.*

Risk Factor	S Additive Index	SR Multiplicative Index
Family History of Breast Cancer	0.66	0.45
Late Party (Age 30+ or Nullipersons)	1.09	0.48
Family History of Breast Cancer and for Late Party	1.07	0.49
Irradiated at First Childbirth	3.21	3.72
Cystic Breast Disease	2.66	1.59
All Benign Breast Disease	1.54	0.95

* Data obtained from Shore et al., 1980.

control group. Characteristics of the study population are given in Table D4.

The results of the analysis of the LSS are similar to the previous studies of radiogenic breast cancer in that:

1) disease incidence increased with dose;

2) latency period decreased with increasing age at irradiation;

3) excess incidence continues (and increases) throughout the follow up period; and

4) the distribution of time between exposure and cancer is similar for irradiated (>100 cGy) and unirradiated groups.

Some differences are seen between the results of this study and those of the fluoroscopy and mastitis studies in that a deficit of cancers is seen in women irradiated between 40-49 years of age. A nonsignificant excess of cancers is seen in women exposed after age 50 for which there is no comparable data in the other series. It has been suggested (49) that the deficit in the 40-49 age interval may be due to the induction of early menopause (a known protective factor for breast cancer) by the (whole body) irradiation. The greatest excess incidence, however, is seen in women aged 10-19 at irradiation which is in accord with the other series.

Analysis comparing additive and multiplicative models, controlling for age at first exposure, shows that neither model convincingly fits the data. On balance, the relative risks appear to be more stable than the absolute risks, although this finding cannot be considered conclusive.

The Japanese age-specific incidence rates of breast cancer are lower than those in North America and, thus, it is questionable whether data from Japanese women are applicable to

Caucasians. Three possible hypotheses for this difference are:

a) Japanese women are exposed to lower levels of carcinogens than western women;

b) Japanese women are less susceptible to potential carcinogens; and

c) a combination of (a) and (b).

Migrant studies of women of Japanese descent resident in North America show them to have rates of breast cancer greater than women in Japan. This observation suggests that hypothesis (b) is unlikely. If we assume (for the purpose of simplicity) that hypothesis (a) is true, then the additive model would predict that excess incidence is the same in Japanese and North American studies, whereas the multiplicative model would predict that the relative risks are the same. A parallel analysis of three series (49) found that fitting an additive model gave a lower linear dose-effect in the Japanese when compared to the two other series (Rochester mastitis, Massachusetts fluoroscopy). Fitting a multiplicative model indicated a higher relative risk for radiation exposure in the Japanese data than in the other series. The results of the comparison of these three series, therefore, does not seem to favour either the additive or multiplicative model.

2.2.3 Benign Breast Series

Baral et al (50) reported the incidence of breast cancer in a group of 1,023 Swedish women irradiated for fibroadenomatosis, acute and chronic mastitis, and unilateral breast hypertrophy (see Table D4). Breast doses were estimated using information on delivered doses from the patients' medical records and assuming the breast in each case to be of average size (when the breast was partially irradiated). The main concern relating to this study is the lack of an

adequate control group. In this study population incidence rates were used to produce expected numbers and compared with the observed. Since the majority of women were treated for benign breast disease, the possibility exists that this condition may predispose to subsequent breast cancer. This set of data has not been as comprehensively analyzed as others and is not as valuable as the previously discussed studies. Generally, the results are in accord with previous studies since: (1) the incidence rate for dose increases with earlier age at first exposure; and (2) the latent period decreases with later age at exposure. A finding of this study, which is at variance with the other studies, is the observation that the average time between exposure and diagnosis decreases with increasing dose. This finding is not compatible with the multiplicative model which predicts that this distribution should not depend on dose. Unfortunately, the analysis of this data does not permit a detailed comparison with respect to the additive and multiplicative models.

2.3 Summary

Two large series of women undergoing fluoroscopy for treatment of tuberculosis have been followed: one in Massachusetts, where 1,020 women ranging in age from 15 to 50 have been followed for up to 45 years, and one in Canada, following 11,315 women aged between 10 and 50 years at time of treatment therapy for approximately 34 years. The Massachusetts study was an incidence study, and the control group consisted of 700 women with tuberculosis who were not irradiated. Breast cancer mortality data from the Canadian group were compared to national breast cancer mortality rates. The major limitation in both these studies is the uncertainty in estimating individual radiation exposures.

Approximately 600 women irradiated for acute post-partum mastitis in New York have been followed for up to 37 years (44). Three control groups were also followed: one of acute

post-partum mastitis patients who had not been irradiated, and two of sisters of both mastitis groups, for a total of approximately 1,200 control women. Although the dosage information is well documented in this study, the fact that these women were lactating at time of irradiation raises the concern that the radiosensitivity of the breast may be different and, therefore, the results would not necessarily be generalizable.

The LSS of the Japanese atomic bomb survivors has published results on the breast cancer occurrence in 63,300 women followed for the period 1950 - 1980 (36 years since exposure) (48,51,52). The main problems in using these results are the uncertainty in the absorbed doses and the lack of generalizability of results from Japanese to Caucasian women.

Results of the studies differ somewhat - overall risk estimates from the A-bomb studies are lower than those of the studies of therapeutically exposed women, and a relationship between latent period and dose seen in one medical series (50) was not evident in the A-bomb survivors, the mastitis series and the fluoroscopy series (49). Parallel analysis of the results of the A-bomb study, the New York study of post-partum mastitis patients, and the Massachusetts fluoroscopy patients by Land et al (49) has, however, been able to show that these three studies yielded reasonably consistent results. The reanalyzed data showed that risk of radiogenic cancer increased with dose in an approximately linear fashion, and that risk depended on age at exposure, and followed the same temporal pattern of occurrence as did breast cancer rates in the appropriate non-exposed female population. These results hold for the female population aged 10 to 40 at time of irradiation; exposed children have not been followed sufficiently long enough to reach the age at which breast cancer risks are likely to become significant. Since the spontaneous breast cancer experience of Japanese and western women differs after age 40, further

follow-up of these studies is necessary to determine the radiation-induced breast cancer experience in older cohorts in these two populations. So far, no information is available on whether the excess radiogenic breast cancer risk extends to the end of life.

In summary, evidence from studies of radiogenic breast cancer do not overwhelmingly favour either the absolute or relative risk models. On balance results seem more in accord with the relative risk than the absolute model. No population exposed at a young age has been followed until death and thus the persistence of carcinogenic effects through life remains open to speculation. These questions will be addressed by further analysis of existing study cohorts as increasing follow up becomes available.

3. Other Epithelial Cancer

The Life Span Study of atomic bomb survivors and the British ankylosing spondylitis study have analyzed the radiation-induced mortality from solid epithelial tumours of non-sex specific sites. The pattern of excess risk parallels that for lung cancer and the main findings are discussed below.

3.1 Life Span Study of Atomic Bomb Survivors

The latest results of mortality follow-up of the Life Span Study sample of 82,000 survivors of the atomic bombs in Japan, encompassing 28 years of follow-up from 1950 to 1978 (25), were as follows:

1) an excess risk of cancer mortality was seen for cancers of the stomach, esophagus, urinary tract, and colon, but not for cancer of the rectum;

2) the excess risk of cancers other than leukemia appears only at the age at which these cancers would normally develop;

3) no shortening of the latent period was observed for solid tumours such as cancers of the stomach, esophagus, or colon; and

4) the radiation-induced cancers seem to develop proportionally to the age-specific background cancer rate.

Therefore, the data on radiation-induced solid tumours other than lung cancer is generally consistent with that for cancer of the lung, and supports a relative-risk model for carcinogenesis. The lack of an excess for cancer of the rectum in contrast to the other solid tumours may be due to the fact that not enough members of the cohort have reached the age at which this cancer normally develops.

3.2 The Ankylosing Spondylitis Study

The 14,111 AS patients treated in England and Wales with a single course of x-ray therapy between 1935 and 1954 were followed until 1970 (26). Cancers of the esophagus, stomach and colon were observed and the following results were noted:

1) an excess of all these solid tumours was observed from nine years after treatment, and continued after more than 20 years of follow-up;

2) the excess death rate was more or less constant from nine to twenty years after treatment; and

3) the increased risk was related to age at time of treatment, with those irradiated at ages 55 or over exhibiting a higher excess death rate. There was no change in the ratio with age.

4. Leukemia

Leukemia has been shown to be composed of a number of different subtypes which possess differing patterns of age-

incidence, sex ratio, and response to therapy. We will employ the categorization of disease into four major types: ALL - Acute Lymphocytic Leukemia, ANL - Acute Non-lymphocytic Leukemia, CLL - Chronic Lymphocytic Leukemia, and CML - Chronic Myelocytic Leukemia. Differences in the age-incidence rates and therapeutic response pose certain problems in the analysis of radiation-induced leukemia:

1) Studies of mortality in exposed individuals may be insensitive for leukemia subtypes which show good response to treatment;

2) Analysis of all leukemias may conceal important differences in susceptibility of individual subtypes; and

3) In its most simple form (no latent period), the additive model for each subtype implies an additive model for all leukemias. In contrast, the analogous multiplicative model for subtypes does <u>not</u>, in general, imply a multiplicative model for all leukemias.

The preceding difficulties may cause further problems since they may cause confusion between the models when analyzing overall leukemia incidence. For example, it is possible to produce theoretical examples where each subtype follows the relative risk model for specific age ranges but the overall rate has an almost constant difference between exposed and unexposed (absolute model) individuals at their same ages. Of course the phenomenon can arise in any tumour but it is most marked in the case of leukemia since it is composed of a number of distinct subtypes with distinctly different behaviour.

The preceding comments place strong requirements on the data to be used for testing the suitability of either the relative risk or absolute models of risk. Of the studies avail-

able only the life span study (LSS) (53) offers sufficiently detailed information on disease subtypes. We will also present findings from the series of British patients treated for ankylosing spondylitis (26,27).

As discussed previously, the LSS represents observations on groups exposed to a mixture of x-rays and neutrons. Analysis using the T65 estimates of dose for each component indicates (54) that the RBE of neutrons (for carcinogenesis) exceeds that of x-rays and that the magnitude of this difference is dose-dependent. Analysis of dose-response for incident cases has been conducted separately for acute leukemia (AL) and chronic granulocytic leukemia (CGL) indicated a differing response between these two types with CGL showing a stronger relationship with neutron dose than did AL. The precise form of the dose-response curve is uncertain, due in part to insufficient data and uncertainties in dose. The data, however, do display an increasing risk with increasing dose in both cities (5,55). The data also indicate that excess (additive risk) depends upon age at exposure with the greatest effect being seen in those irradiated in the range 0-9 years and those irradiated at age 50+ years. A striking feature of the development of radiation-induced leukemia is its "wave"-like pattern of appearance after exposure. Excess acute leukemia appears 2 years after irradiation and the excess increases rapidly up to a maximum. The time to reach this maximum appears to vary with age of exposure and the type of leukemia under consideration. Although data are naturally rather sparse, it appears that for those who develop acute leukemia, the maximum excess incidence increases from about 5 years after exposure for those irradiated at less than 15 years of age, and about 20 years for those irradiated at age 45+. For those developing CGL, a similar relationship exists although the data are not as convincing. Although a similar analysis based on relative risk changes with age at exposure and time since exposure has not been presented, it does appear that the relative

risks show a similar variation to those of the additive excess risks. Thus, it would appear that the data from the LSS are incompatible with either a simple additive or multiplicative model since the time evolution of radiation-induced disease does not show a pattern compatible with either model.

The second set of data we will consider is the analysis of a group of British patients treated with x-rays for ankylosing spondylitis. This study used death certificates in which it was not possible to identify the type of leukemia (although medical histories were reviewed where feasible). In a recent analysis of this cohort, attention has been restricted to the first treatment series received by the subjects (26). Those receiving two or more series of x-ray treatments were treated as censored (i.e. removed from follow-up) 18 months from the date of their second treatment and all dose estimates were based on their first series of therapy. Dosimetry was not done on the whole population but was carried out on a 1 in 15 sample. Using the estimated mean dose for the group, this study does produce estimates of excess risk of death from leukemia for doses which are not greatly different from those found in the LSS. A gradient of relative risk with age at exposure was not found in this study, although a gradient in additive excess risk was seen. Analysis, after standardization for age at exposure, showed a decreasing relative risk with time since exposure. No excess relative risk was seen beyond 18 years after exposure although data is sparse in this region. These data, therefore, show the same wave-like incidence pattern of excess leukemia seen in the LSS. From this, we would conclude that these data do not fit either the absolute or relative risk model without including a time after which risk is terminated.

Simultaneous analysis of both the LSS and the ASS using a multiplicative model has been undertaken (56). In order to

do this, only data on individuals receiving in excess of 100 cGy or less than 9 cGy (T65 estimates) were utilized from the LSS. In this analysis, dose was ignored and the >100 cGy was considered as an irradiated group and those receiving 9 cGy or less being treated as a control (unirradiated) group. A general linear model approach was utilized with Poisson errors and terms reflecting age at exposure and years since exposure were included. This analysis reconfirmed the previous analysis showing that excess (relative) risk declines with years since exposure although an excess appears to persist up to the level of follow up (31 years) for the LSS.

A more recent analysis using the same data has fit a general statistical model in which an additive and multiplicative model are special cases (57,58,59). Within this single framework the authors found that a multiplicative model where risk declined with time since exposure was compatible with the data, but that a similar additive risk model was incompatible with the data. Restricting attention to the data from Hiroshima produced exactly the opposite results with the data being compatible with an additive model and not a relative risk model. It is not easy to interpret these contradictory findings, although they may in part arise from the differing age-incidence patterns of the leukemia subtypes in Britain and Japan. As previously remarked this kind of inhomogeneity leads to problems in the application of the relative risk model. More significantly the authors have included a linear term in time since exposure so that the models fitted do not correspond either to the absolute or relative risk models under consideration here. The implication from this analysis would therefore seem to be that neither the absolute nor the relative risk model is suitable for predicting risk of leukemia after exposure to radiation.

Although several other studies of radiation-induced leukemia have been undertaken, they are not helpful, since they relate to prolonged exposure (of occupational origin), thus

making it difficult to analyze the effects of time since exposure (which is critical for discrimination between the additive and multiplicative models). Where it has been examined, in appropriate studies, leukemia appears to follow the same wave-like pattern of incidence (5,60).

5. Studies of Multiple Sites

Two of the previously described studies (LSS and AS) have examined data from multiple sites simultaneously. The advantage of this approach is clear in that they increase the number of cases of disease available for analysis. However care must be taken in the selection of such sites since the inclusion of organs of varying radiosensitivity may prove counterproductive. Thus the aggregation of sites on the basis of dosage, as in an analysis of the AS study (26), leads to a situation in which sites with apparently differing radiosensitivities are pooled. Analysis of the relative risk model showed that it was not incompatible with the data. Similar analysis of the absolute risk model was not made, but calculation of approximate confidence intervals for the excess risk at different follow-up intervals are quite wide so that this model would probably not be rejected either.

The analysis of Muirhead and Darby (57) has examined the data from the LSS (Hiroshima) and the AS study for the following sites: pharynx, esophagus, stomach, pancreas, larynx, lung (including pleura) and skin. Strata were constructed for sex, age at exposure and time since exposure and an additive and multiplicative model were compared using a general model. The resulting analysis in each of the two studies favoured the relative risk model and rejected the absolute risk model. Thus if it is necessary to choose between the two models then this analysis would suggest that the relative risk model is to be preferred. The authors also concluded that the inclusion of other factors including sex, age at exposure, and time since exposure (which would modify

the model) did not improve the fit of the model. Others have questioned the parameterization of these other factors (58,59); however, this analysis presents considerable evidence for the relative risk model as a single model for the prediction of risk of cancer (for the sites considered).

Another analysis of the LSS data, using all cancer mortality, has also come to the conclusion that generally the relative risk model provides a better fit than the absolute risk model (61). However, Cohen feels that both models are unsatisfactory in that they give no explanation as to why the relative risk decreases with increasing age at irradiation. Cohen also indicates that an additive model with variable latent period would fit the data as well as the relative risk model. This may be true, but it must be recognized that any generalization of either model inevitably makes each model more flexible, so that they can more closely fit any data and will be more difficult to distinguish.

Another study which has examined the development of radiation induced cancer is a recent study of individuals treated for cervical cancer (62). Although this study involved large numbers of women (182,000), comparatively few cancers which could be attributable to radiation were observed. Given the advanced age of this cohort there were many spontaneous cancers seen so that the "signal to noise" ratio was very low in this data. The small number of radiogenic cancers was partially attributable to the age at radiation since most tissues show declining radiosensitivity at advanced ages. A notable exception is leukemia which was quite clearly shown to occur in excess. However, as indicated earlier, leukemia does not seem to follow either the additive or relative risk model so that little information on these models can be obtained from the analysis of this series.

In summary, the studies discussed present no situation (except possibly for individual age at exposure strata in each study) where the absolute model is superior to the

relative risk model. In contrast, many of the analyzes indicate the superiority of the relative risk model. Of the studies discussed most weight must be placed on that of Muirhead and Darby (57) since: 1) it groups tumour sites with similar age incidence patterns, 2) it analyzes data from two major studies (LSS and AS) and 3) it uses a single statistical model.

E. CONCLUSION

For the non-sex-specific epithelial tumours the majority of evidence from human data tends to favour the relative risk model over the absolute risk model. Isolated exceptions exist, but there seems little reason from either considerations of biology or data analysis to use the absolute model as a general predictor. Consideration of mathematical models of carcinogenesis lead to a similar conclusion. These models (Armitage-Doll and Moolgavkar-Venzon) do not always result in predictions exactly in accord with the relative risk model, but the predictions are closer to the pattern predicted by the relative risk model than that of the absolute risk model. In contrast, the leukogenic effect of radiation follows a wave-like pattern which does not parallel the natural incidence rate of the disease. However, multiplicative models do fit the data better than additive ones if the relative risk is permitted to decline with increasing time since exposure. In the case of leukemia the absolute risk model fit the data as well if not better than the relative risk model. However, in this case the difference between the numerical predictions of the two models is small since both predict excess risk over a comparatively short period.

The information available for radiogenic effects on the female breast are as extensive as for any other cancer site. Here the bulk of evidence favours the relative risk model although none of the studies has yet supplied strong evidence against the absolute risk model. Overall, it would appear that the relative risk model is better supported by the data for most types of cancer than the absolute risk model and is the preferred one of the two for risk projection.

1. Projection of Lifetime Risk

It has been pointed out by a number of authors that use of

the relative risk models leads to greater lifetime numbers of projected cancers than the absolute model for almost every site. It has been shown (57) that the large difference in the number of cancers predicted is not reflected in the number of years of life lost due to cancer where the increase is proportionately smaller because such cancers occur at more advanced ages. Clearly the magnitude of projected differences between these two models depends upon the outcome under consideration. Furthermore, the magnitude of the projected differences in the number of cancers depends strongly upon the use of current estimates of radiogenic risk for each model. As longer follow-up becomes available on cohorts exposed to radiation the absolute and relative risk will change so that each fits the data as well as it can. Therefore, continuing follow-up of the cohorts identified in this report is necessary in order to refine the estimates of radiogenic risk. Not only will more data allow one to distinguish better between the models, but it will also cause the estimates of lifetime risk for the two models to converge (in populations similar to that of the study population). This emphasizes that the major difference between the two models when follow-up is for a lifetime, as distinct from any particular set of parameter values of these models, is not the number of cancers they predict but when the excess cancer will occur.

In much modelling of health risk it is advisable to be conservative. By this it is intended that for any exposure (with a potentially adverse effect) subject to control, a model of its impact should, where uncertainty exists, not underestimate its effect -- the purpose of this being to set exposure limits whereby "safety" is ensured. For tumours with increasing age-incidence rates the relative risk model is more conservative than the absolute model for the projected number of cancers where current estimates are used. However this situation can change. For example, as mentioned previously, complete follow-up to death of an irradiated

cohort would give similar lifetime estimates of cancer from each model when applied to a similar population (i.e., similar in risk factors for that cancer). Then the absolute model would predict more years of life lost to radiogenic cancer than the relative risk model (for cancers whose age-specific incidence rates increase).

In attempting to use either the additive or multiplicative model for projections in populations exposed to radiation one must also model (or know) other determinants of radiation risk. Prominent among these is the dose-response function. It is clear that considerable uncertainty still exists on the nature of this function, so that, in most cases, uncertainty will exist in any projections. If we assume that these quantities are reasonably well known, and the risk projection model is known (either relative or absolute), then the largest uncertainty in future projections is the parameter values themselves. The difficulty in distinguishing the relative risk from the absolute models testifies to the amount of variability in the data. Thus estimates for the parameter values for these models have wide confidence intervals attached to them. For many strata, defined by age at exposure and sex, the differences between projected lifetime risks using relative and absolute models are similar to differences using the most extreme parameter values compatible with the data (95% confidence limits) for each model. Selection of the appropriate model will therefore not necessarily lead to accurate estimates of lifetime risk and considerable uncertainty will still remain.

Data currently available indicate that, for solid tumours, the relative risk model is to be preferred to the additive model. Projections of future risk of radiogenic cancer thus require accurate knowledge of the background incidence rates for each site. This essentially requires two (overlapping) steps: 1) establishing an appropriate method for calculating the incidence rates in the population and 2) projecting it

into the future. The first step may merely consist of using the appropriate sex and age-specific incidence rates of the general population. However, the target population may not be representative of the general population for some important risk factor for cancer (smoking history, reproductive history, etc). This requires knowledge of the distribution of such characteristics in both the target and general populations. Secondly, projection of incidence rates into the future requires knowledge of cohort trends in cancer incidence. For example, lung cancer rates in men are expected to decline whilst those in women are expected to rise. Cross-sectional incidence rates will therefore not be sufficient for this purpose.

Finally, a convincing model for the projection of risk can only come from a good understanding of the nature of radiation carcinogenesis. The relative risk and absolute risk models are not constructed using plausible models of carcinogenesis and may be viewed as "rules of thumb" whose accuracy is yet to be proven. Increasing analysis of current data sets will ultimately discriminate between them although the most likely result is the identification of more complex models of behaviour which those models approximate.

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APPENDIX A

THE MODEL OF MOOLGAVKAR AND VENZON

Introduction

The Moolgavkar-Venzon model is a two stage model for the development of cancer. In order to become malignant a cell must first pass through an intermediate stage where such cells grow as a birth and death process. Transitions between the stages (normal to intermediate, intermediate to malignant) occur at constant rates. Malignant cells are assumed always to grow to form a tumour. Normal cells are assumed to grow throughout life according to some known mathematical law. All cells are assumed to behave independently of others.

General Structure of the Moolgavkar-Venzon Model

To simplify development we will assume that a single malignant cell once created does not grow. Since we are only interested in the presence or absence of malignant cells (which corresponds to tumour development) this will not affect deductions regarding the incidence of cancer. Let $Z(t)$ and $W(t)$ be the number of intermediate and malignant cells at time t and let $M_1(t)$ be the number of transitions from the normal to the intermediate state in the interval $(0,t)$. Define $\phi(z,w;t',t")$ to be the probability generating function for the number of intermediate and malignant cells which develop from new transitions in the interval $(t',t")$, that is

$$\phi(z,w;t',t") = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} P\{Z(t")=i, W(t")=j \mid Z(t')=0, W(t')=0\} z^i w^j$$

The incidence rate of disease $I(t,0)$ at time t is given by

$$I(t,0) = -\frac{\partial}{\partial t} \ln \phi(1,0;0,t). \qquad [1]$$

From the general theory of Filtered Poisson Processes (Parzen, 1962), the probability generating function is given by

$$\phi(z,w;t',t'') = \exp\{\int_{t'}^{t''} \alpha_1(s)X(s)[\phi_1(z,w;t''-s)-1]ds\} \quad [2]$$

where $\alpha_1(s)$ is the transition rate from normal to intermediate, $X(s)$ is the growth function of the normal cells and $\phi_1(z,w;t)$ is the probability generating function for the number of intermediate and malignant cells derived from a single intermediate cell present at time t=0, i.e.

$$\phi_1(z,w;t) = \sum_{i=0}^{\infty}\sum_{j=0}^{\infty} P\{Z(t)=i,\ W(t)=j \mid Z(0)=1,\ W(0)=0, M_1(t)=0\}z^i w^j$$

Since the cells behave independently then quite generally from any t',t'' such that t''>t'>0 we have,

$$\phi(z,w;0,t'') = \phi(z,w;t',t'')\phi(\phi_1(z,w;t''-t'),\ w;0,t') \quad [3]$$

Using standard arguments it is a straightforward matter to show that

$$\phi_1(z,w;t) = \frac{(d_1+\alpha_2 w)(1-e^{-kt}) - z(s_1 - s_2 e^{-kt})}{s_2 - s_1 e^{-kt} - zb_1(1-e^{-kt})} \quad [4]$$

where

$$s_1 = \frac{1}{2}[\alpha_2 + b_1 + d_1 + k],\ s_2 = s_1 - k$$

and

$$k = \sqrt{(\alpha_2 + b_1 + d_1)^2 - 4b_1(d_1 + \alpha_2 w)}$$

If the second transition rate (α_2) is sufficiently small with respect to the difference in the growth parameters for the intermediate cells, that is $2\alpha_2 b_1 << (b_1-d_1)^2$, then

$$I(t,0) \approx e^{-kt}\int_0^t \alpha_1(s)\alpha_2 X(s)e^{ks}ds$$

<u>Incorporating the Effect of Carcinogens - Continuous Exposure</u>

In common with the Armitage-Doll model the effect of carcinogens can be incorporated by assuming that they modify the value of one or both of the transition rate parameters α_1 or

α_2. The effect of certain carcinogens may also be incorporated by assuming that they effect the intermediate growth parameters b_1 and d_1. The former case corresponds approximately to modeling 'initiators' and the latter to 'promoters'.

Equations [1], [2], [3] and [4] may then be used to calculate the effect of carcinogens with the assumption that exposure to a carcinogen over an interval effects the values α_1 and α_2 over that interval. For example consider the effect of exposure to a carcinogen over the interval (t_1,t_2) on the incidence rate of cancer at age $t(>t_2)$. Then from equation [3] we have,

$$\phi(z,w;0,t) = \phi(z,w;t_2,t)\phi^*(\phi_1(z,w;t-t_2),w;t_1,t_2) \cdot\phi(\phi_1^*(\phi_1(z,w;t-t_2),w;t_2-t_1),w;0,t_1) \quad [5]$$

where ϕ^*,ϕ_1^* are calculated as in equations [2] and [4] with the parameter values for the carcinogenic exposure. Examining equation [5] it is easily seen that the determination of the incidence rate, as given in equation [1], requires the evaluation of four functions;

$\frac{\partial}{\partial t}\ln\phi(z,w;t',t)$, $\frac{\partial}{\partial z}\ln\phi(z,w;t't")$, $\frac{\partial}{\partial t}\phi_1(z,w;t)$ and $\frac{\partial}{\partial z}\phi_1(z,w;t')$

where t',t" may take arbitrary values. These four functions are given as follows:

$$\frac{\partial}{\partial t}\ln\phi(z,w;t',t") = \alpha_1(t)X(t)(z-1)+\int_{t'}^{t}\alpha_1(s)X(s)\frac{\partial}{\partial t}\phi_1(z,w;t-s)ds$$

$$\frac{\partial}{\partial z}\ln\phi(z,w;t',t") = \int_{t'}^{t'}\alpha_1(s)X(s)\frac{\partial}{\partial z}\phi_1(z,w;t"-s)ds$$

$$\frac{\partial}{\partial z}\alpha_1(z,w;t) = k^2e^{-kt}[s_2 - s_1e^{-kt} - zb_1(1-e^{-kt})]^{-2}$$

and

$$\frac{\partial}{\partial t}\phi_1(z,w;t') = -\frac{s_1 - zb_1)(s_2 - zb_1)}{b_1}\frac{\partial}{\partial z}\phi_1(z,w;t')$$

Generally the integrals in the above expressions may not be calculated explicitly but require numeric integration.

Effect of Carcinogens - Instantaneous Exposure

In many settings exposure to radiation occurs over a short period. In such cases it is reasonable to consider radia-

tion as a pulse. This may be modeled by assuming that a proportion of cells instantaneously transit between states. Let p(d) be the probability that a single normal intermediate cell will become malignant after exposure to a dose d of radiation. If radiation exposure occurs at time t_1 then

$$\Phi(z,w;0,t_1) = \psi_1(z,w;t_1)\Phi(\psi_2(z,w;t_1),w;0,t_1^-) \qquad [6]$$

where

$$\psi_1(z,w;t_1) = [1 - p(d) + p(d)\ z]^{[X(t_1)]}$$

and

$$\psi_2(z,w;t_1) = [1 - q(d)]\ z + q(d)w$$

Equation [6] may then be used with equations [1], [2] and [3] to calculate the incidence rate at subsequent age t. Clearly the effect of instantaneous transitions between the intermediate and malignant state is to produce a pulse of tumours which will be subsequently followed by a deficit (although this deficit may be small). The period over which the pulse of radiogenic tumours are manifest will depend on the time for the tumour to become clinically manifest and the variability in this quantity. In order to calculate the incidence rate we also require the following quantities:

$$\frac{\partial}{\partial z}\ \ell n\psi_1(z,w;t) = \frac{X(t)p(d)}{1 - p(d) + p(d)z}$$

and

$$\frac{\partial}{\partial z}\ \psi_2(z,w;t) = 1 - q(d)$$